The following recommendations are dynamic and will be revised, as new clinical data become available. These criteria are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

Alzheimer's disease (AD) is the most common cause of dementia in North America. The first clinical signs of AD are impairments of memory, language and visuospatial function, some of which can be explained by loss of cholinergic neurons in the basal forebrain. This loss contributes to the symptom development of AD. The clinical diagnosis of AD can be made using the criteria of the Diagnostic and Statistical Manual – IV (American Psychiatric Association, 1994)[40]. Once the diagnosis of AD has been made, the severity of the dementia can be estimated and monitored using a cognitive instrument such as the Mini-Mental State Examination (MMSE).[39] The main pharmacological approach to limiting cognitive and functional decline in AD is to increase synaptic levels of acetylcholine through use of cholinesterase inhibitors (CIs). Treatment of AD should take into account concerns about quality of life for the patient and for members of his/her family. Therefore, it is important to respect patient and family preferences when making treatment recommendations. Since these agents are costly and are sometimes associated with side effects, their role in AD management must be clearly defined. The use of CI in other disease states such as Lewy Body and vascular dementia is not addressed by this document.

The CIs, donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon®) are modestly effective in delaying cognitive and functional decline in patients with mild to moderate AD.[1-4, 7-21] There is no level I evidence* to demonstrate superiority amongst the agents. Dose and titration schedules differ among the agents (see Table 1). Generally the agents are well tolerated with common adverse effects managed with titration and dose adjustments. CIs have been shown to offer benefit by delaying nursing home placement or by reducing costs of care in the home.[22-36]In one published trial, donepezil has also been shown to delay functional decline in patients with moderate to severe AD who are still living in the community.[12] Data on the effects of CI use in nursing home patients with mild to moderate disease are not available. Therefore, the initiation of CI in the nursing home population must consider the cost effectiveness of these agents and paucity of data on their benefit in this group. Tacrine (Cognex®) is no longer used as a first-line agent in AD because of the risk of hepatotoxicity. There is insufficient evidence* to support the initiation of CIs in AD patients with severe dementia (MMSE<10). **CI therapy should be discontinued if there is evidence of a) poor compliance; b) persistent side effects; c) mutual agreement between caregiver and provider. A tapered discontinuation is recommended in a) progression to severe dementia (MMSE<10); b) development of a concomitant contraindicated medical condition (see algorithm); c) permanent loss of caregiver or d) permanent institutionalization for severe dementia with functional loss.** CI therapy may be re-initiated in patients where there is evidence of a rapid decline upon discontinuation of CI therapy. There is insufficient evidence* to support switching between CI's if one agent is not tolerated or is ineffective.[6]

Table 1: Cholinesterase Inhibitors#

Drug	Initial dose	Titration schedule every	Recommended dose	Cost/month	Minimum Therapeutic Dose	Formulations
Donepezil** Aricept®	5 mg QD	4 weeks	10 mg QD	$76.50	5 mg QD	Tablets: 5,10 mg
Galantamine Reminyl®	4 mg BID	4 weeks	12 mg BID	$78.00	8 mg BID	Tablets:4,8,12 mg Oral liquid 4mg/ml
Rivastigmine Exelon®	1.5mg BID	4 weeks	6mg BID	$80.40	3 mg BID	Capsules: 1.5,3,4.5, 6 mg Oral liquid 2mg/ml

#Cognex® (tacrine) is not included in this table due to hepatoxicity risk
** Currently only agent on VA National Formulary
QD- once daily, BID- twice daily

* **Quality of Evidence**
I: Evidence obtained from at least one properly randomized controlled trial. US Preventative Task Force scale Am J Prev Med 2002;20(3S):21-35.

Algorithm for CI Therapy in Alzheimer's Dementia

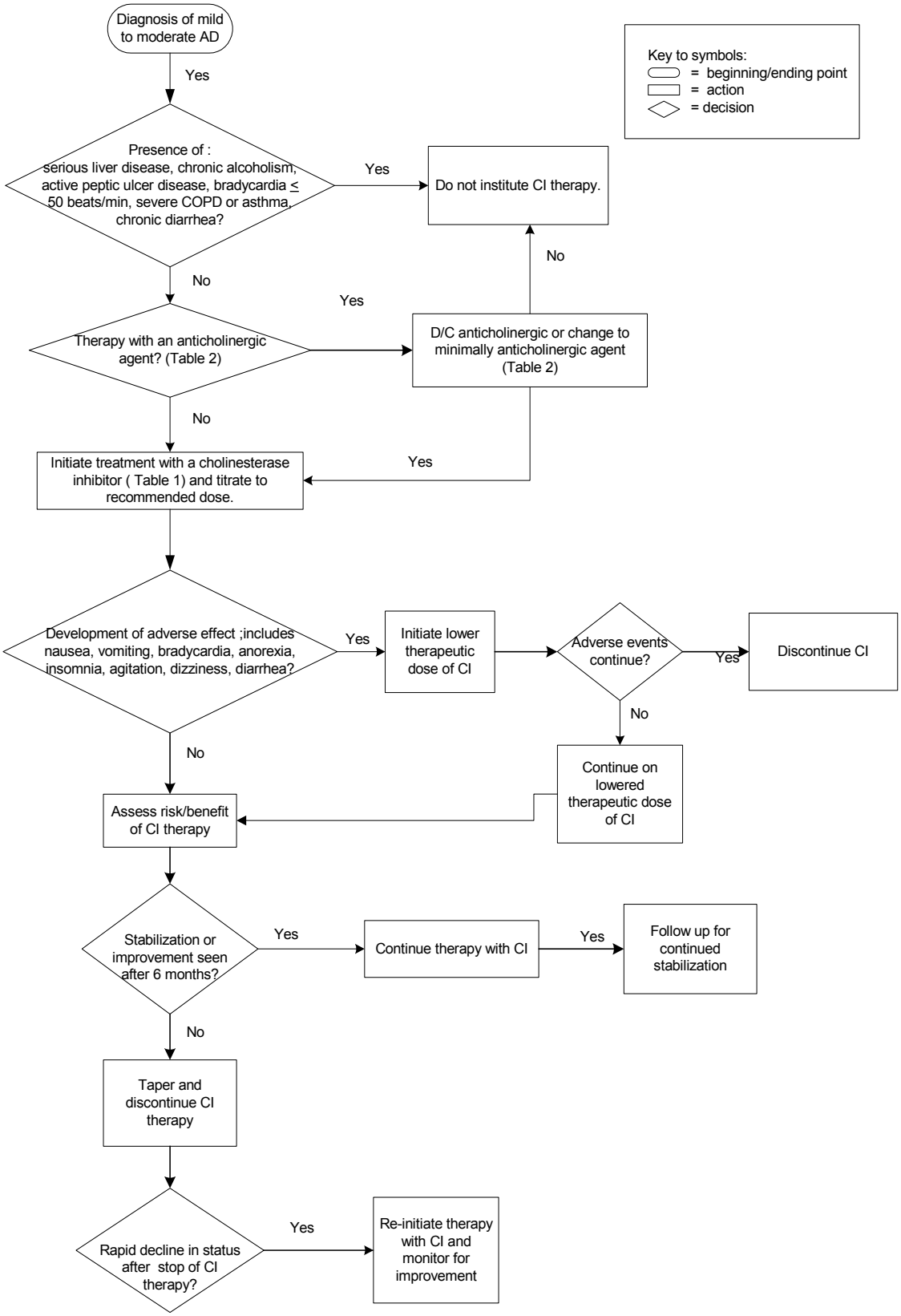

Table 2: Anticholinergic Activity of Selected Agents[@]

Class	none- minimal anticholinergic effect	moderate anticholinergic effect	high anticholinergic effects
Antidepressants	Bupropion, sertraline, paroxetine citalopram, fluoxetine, fluvoxamine	nortriptyline, desipramine , doxepin, maprotiline mirtazapine	amitriptyline, protriptyline, clomipramine, amoxapine, imipramine,
Antiparkinsonian	levodopa, pergolide, pramipexole, ropinirole	amantadine	benztropine, trihexyphenidyl
Antipsychotics	risperidone ziprasidone haloperidol	olanzapine, quetiapine, chlorpromazine, pimozide	clozapine, thioridazine, mesoridazine, promazine, triflupromazine
Antispasmodics		belladonna alkaloids, dicyclomine tolterodine, diphenoxylate	atropine, oxybutynin
Antihistamines	loratadine, fexofenadine, cetirizine	brompheniramine, chlorpheniramine hydroxyzine	clemastine, diphenhydramine, promethazine
Other			meclizine, scopolamine, dimenhydrate, prochlorperazine

[@]It should be remembered that patients with AD are uniquely sensitive to anticholinergic agents and even minimal effects can translate into clinical changes. These agents should be avoided if at all possible.

Table 3: Drug Interactions

Precipitant drug	Object drug	Description
Cimetidine	Galantamine	Bioavailability of galantamine increased by 16%*
Ketoconazole	Galantamine	Galantamine AUC increased 30%*
Paroxetine	Galantamine	Galantamine oral bioavailability increased 40%*
Erythromycin	Galantamine	Galantamine AUC increased 10%*
Donepezil	Furosemide, digoxin, warfarin	Donepezil did not alter the binding of the object drugs
Ketoconazole	Donepezil	Donepezil metabolism may be altered#
Quinidine	Donepezil	Donepezil metabolism may be altered#
CI class	Succinylcholine	Exaggeration of relaxation response

Donepezil and Galantamine are metabolized through both CYP 450 3A4 and 2D6 isoenzymes
Rivastigmine is not extensively metabolized by the cytochrome P450 system
Clinical effects of the interactions are unknown; they are postulated interactions.

* Clinical significance of these interactions is unknown.
AUC-Area Under the Concentration Time Curve

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